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MDS Harris
Science Advancing Health

February 25, 1999

Documents Management Branch (HFA-305)
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Dear Regulators:

As you will see in my comments, I am requesting that this document not go forward until the planned conference between AAPS and the FDA can be held this fall and further information gathered before its final issue.

I appreciate the opportunity to comment and can be contacted at (402-476-2811 concerning any questions relative to my comments.

Sincerely,

James D. Hulse, Ph.D.,
Vice President
Bioanalytical Services

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Enclosure

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Response to the FDA's Guidance for Industry Bioanalytical Methods Validation for Human Studies

General Comments:

This draft guidance generally follows the published outcome from the Crystal City meeting of 1990 but does not address the newer technologies that have become commonplace since that meeting was held nearly a decade ago. There is a workshop being planned by the AAPS in September 1999 to discuss and update that publication. We would request that results of that meeting be included in the preparation of new guidances for industry use. We would therefore ask that this FDA draft guidance be tabled until this can happen.

This guidance seems to add several different components that are not generally accepted nor addressed at the 1990 workshop. History would show that guidances like this one are more widely used than the original intent. It is because of this that we have concerns about the general direction that the guidance may take and the detail it outlines for a number of areas. For example: Although it states early on that it does not apply to non-human pharmacology/toxicology studies, our experience is that it will be applied in this area since these studies are covered under GLP. This document in fact places bioanalytical methods used in human clinical pharmacology studies (page 1, paragraph 1) under adherence to FDA's Good Laboratory Practices (page 2, paragraph 3). GLP specifically states that clinical studies are not covered by GLP practices. Although we know in general that the spirit of GLP is commonly used for these studies, the adherence to absolute GLP application to this work adds unnecessary burden and complication.

There is ambiguity or vagueness in 1) Terminology used. We suggest that a glossary should be used to define terms such as: Selectivity, LLOQ, signal to noise (how it is determined), SOP (or a better term, assay protocols), standard calibrators, dynamic range of standard curve, linearity, spirit of GLP, reproducibility, repeatability, etc. 2) How certain tests or procedures should be carried out. 3) What is merely recommendation vs. what is real acceptance criteria that must be followed.

It is difficult to write a guidance that is detailed enough to be of value but not of such detail as to encumber good scientific judgement. We have tried to give sufficient specifics in this response to be of value. However, our bottom line recommendation is that we should wait for the scientific input from the Crystal City II workshop in September, and then draft a guidance that reflects the general practice of the industry, with the current knowledge of present technology.

Specific Comments:

Section I. Introduction

p. 1 first paragraph: Application of the guidance - The application of this guidance to some human clinical pharmacology studies may be too tight as often early studies are conducted to "learn" about the drug whereas later studies (which are submitted for approvals) are done to "confirm." This guidance should be addressed to confirming studies.

p. 1 second paragraph "applicable to gas chromatography or high-pressure liquid chromatography analytical methods"- In the broad sense, this includes mass spec methods (LC/MS, LC/MS/MS). Issues of LCMS should be addressed before issuance of the guidance. There certainly are concerns to this technology.

This guidance should also apply to other analytical techniques such as immunological and microbiological methods or other biological matrices, ..., although in these cases a higher degree of variability may be observed" - This is vague and undefined. What kind of observed data would be acceptable if variability is higher. Potential variable interpretations on such clauses by the practitioners and FDA reviewers will lead to confusion.

Section II. Background

p. 2, paragraph 1, the term "selectivity" should be used instead of "specificity" and also in other places in the text.

p. 2, paragraph 2: Issue of what can be considered as "minor or major modifications" and what is "full or limited validation" - Minor or major modifications are method-dependent. E.g. Temperature change on chromatography could be either case. General mention of it in a guidance like this, could lead to inappropriate interpretation. A general statement like the following could be used: The study scientist should use scientific judgement to assess the impact of the method modification on the validation, and if certain areas could be affected, experiments should be carried out to re-establish the validity in that area with the modification. A full validation may not always be required as long as rationales are given to what tests are adequate.

p. 2, paragraph 3: GLP specifically state that clinical studies are not covered by those practices. - In general the spirit of GLP is commonly used for these studies. However, the adherence to the absolute GLP in this work, e.g. the requirement of a master schedule and a study director, add unnecessary burden and complication to these studies. The responsibilities for a study director are far reaching.

p. 2, paragraph 3: "The analytical laboratory should have a written set of SOP...sample preparation, and analytical tools, such as methods, reagents, equipment, ..."- SOPs are written on general operation processes in most bioanalytical laboratories. For individual method procedures, they may not be considered as stringent as a SOP. The need of minor modifications has already been discussed. Bioanalytical data in human studies may require possible changes from one study to another. E.g. The standard curve dynamic range may change from one dosage form to another; HPLC components may vary from

one set up to the next; and mobile phase may be optimized slightly from one column lot to another; etc. A written method is important. Having it at an SOP status is not.

Section III. Reference Standard

p. 3, paragraph 1: Master standard and certification of reference standard - The introduction of the "master standard" concept is a novel idea that certainly needs discussion on its practicality. The extension of formulary practice on reference standard to the bioanalytical area can be another unnecessary burden. The need for certification for internal standard and standards for selectivity check should be discussed.

p. 3, paragraph 1: Source of reference standard – The definition of a "reputable commercial source" is vague. Custom-synthesis may or may not be done "by an analytical laboratory or other noncommercial establishment". As long as purity test documentation is available, the source supplier is unimportant.

Section IV. Pre-Study Validation

A. Specificity

p. 3, Last paragraph: "Prestudy validation should include analytical method development and documentation." - Development work should not be included as part of validation because of the constant iterative and interactive changes being made, exhaustive, detailed documentation similar to validation work will be counter-productive.

p. 3, Last paragraph: "blank samples ...from six individuals under controlled conditions, with reference to time of day, food ingestion, and other factors considered important in the intended study." – This is not practical because common source of blank samples are from commercial vendors. This requirement would make control sample collection extremely costly and it would be difficult to verify the documentation of the commercial vendors.

p. 4, first paragraph: blank compared to an aqueous solution of the analyte at a concentration near LOQ. – Not applicable to immunoassay or LCMS where matrix effect could occur and then such comparison would not be valid. Does "aqueous" mean a non-matrix solution?

p. 4, second paragraph: 10% of at least 6 test lots do not show interference. – We recommend 20% to be used, so that 5/6 lots could be acceptable.

p. 4, third paragraph: interfering substance from decomposition products, ..nicotine and OTC drugs and metabolites. – Decomposition products are not easily available. Nicotine and OTC tests should be dependent upon the need of specific study protocol at the discretion of the study director or principal investigator. This statement adds much additional work at questionable value.

B. Calibration Curve

p. 4, fourth paragraph and p.5, next to last paragraph: It will be clearer if the term "standard calibrators" are used for standards used for curve fitting to differentiate the other extra standards (n≥5) used to evaluate precision and accuracy of the LLOQ, ULOQ and mid standard.

p. 4, Linearity – Simple straight line equations are often applicable for simple physicochemical measurement. They are not appropriate for assays that involve bimolecular reactions or interaction mechanism such as immunoassays and some electrospray MS. Weighting the curve or using complex regression equations should not be discouraged if properly validated. Linearity should be defined as the best fit functions, not as "linear" in the literal sense. The acceptable variance vs. concentration range should be defined for each type of assay.

p. 5, sixth paragraph: Not accepting data from an entire curve because the highest or lowest standard is not acceptable – If the QCs are bracketed by other acceptable standards, and all other criteria passed, the curve should be acceptable.

C. Precision, Accuracy and Recovery

p. 6, first paragraph: accuracy and acceptance criteria of calibration standards. – It is not clear as to what happens to standards that are beyond the acceptance criteria.

p. 6, second paragraph: recoveries required to be above 50 or 60% – The amount of recovery should not impact the assay performance as long as it is consistent. Recovery is performed for the sake of method development, and it is not crucial for method validation. Requirements to determine recovery should either be eliminated from the guidance or no defined amount should be required for acceptance. For LCMS methods and immunoassays, recovery may not be compared to a pure authentic standard (p. 6, second paragraph) because of possible matrix effect. It is better to compare the signal of the spiked blank control before extraction vs. that of spiked post-extraction.

D. Quality Control Samples

p. 6 third paragraph: Using a different source of biological matrix for each validation batch. This requirement should be eliminated because of the following reasons: 1). Lot-to lot variability is already tested with the ≥6 lots with and without spiking a known amount of the analyte and by the QCs prepared from a pooled matrix vs. standards that are prepared periodically from various matrix lots. Using a different source of biological matrix for each validation batch will not add additional information. 2). Instead of obtaining new information, it will confuse the issue of interday variability by adding other variables of a different matrix lot with a different preparation. 3). This practice does not reflect that of clinical sample analysis where QCs are not prepared daily but only once in a single batch before the study starts.

p. 6 third paragraph: What is meant by (7) "reference standard". Please clarify.

p. 6 third paragraph: LOQ QC sample – We suggest that extra standards at the LOQ be tested instead of preparation of an LOQ QC from the QC standard stock. Using the LOQ standards ($n \geq 5$), it will avoid discrepancy from a separate weighing and provide real assessment on the precision and accuracy at the LOQ of the method itself.

E. Stability

p. 7, paragraph 2: "Stability ... is relevant only to that ...container system and should not be extrapolated". - This implies that every time a container type or even manufacturer batch changes (polypropylene vs. polyethylene, plastic to glass, etc.) the stability work needs to be repeated. We urge that details of stability tests of sample collection and storage during validation should be left to the judgement of the scientist to cover stability issues that one can anticipate for each particular analyte and not to be "micro-guidelined".

p. 7, bottom paragraph: Freeze and Thaw Stability –stability QCs should be thawed "unassisted and at room temperature" and "transferred back to the original freezer and kept refrozen for 12 to 24 hours.". Not all analytes are thawed at room temperature, some may require fast thawing and then kept in an ice-water bath, some may require a fast freezing step instead of a slow freeze inside a freezer. Therefore, we suggest that it should be stated that QCs are thawed, kept at the similar bench environment, and refrozen under the same conditions as will be used for study samples.

p. 8, third paragraph: Stock Solution Stability – This stability should be analyte specific and the test detail of time span and temperature should be up to the discretion of the scientist. *p. 8 fourth paragraph: Autosampler Stability – "The stability of both the drug and the internal standard should be evaluated in validation samples under these conditions by determining concentrations on the basis of* ***original calibration standards.***"- Comparison to the original calibration standards is not practical for LCMS methods because of system drifts. In practice, if a curve is to be re-injected, or injection is to be delayed, the entire curve including the calibration standards will be performed. There is no need to compare them to the original calibration standards as long as the internal standard tracks the analyte in whatever possible degradation and/or system signal drift.

V. In-Study Validation

p. 9, bottom paragraph: - Need clarification and rational of "difficult procedure with an labile analyte", why multiple analyses would give better estimate.- High variability is not limited to difficult procedures.

p. 10, fourth paragraph: Reassay should be done in triplicate if sample volume allows.

p. 10, fifth paragraph: bound laboratory notebook - With the electronic age currently present, a requirement for a bound notebook is questionable.

p. 10 fifth paragraph: specific SOPs: Clarification is needed for the meaning of SOPs. If that means the analytical method, we suggest that a different terminology be used (see above on p.2 paragraph 3).

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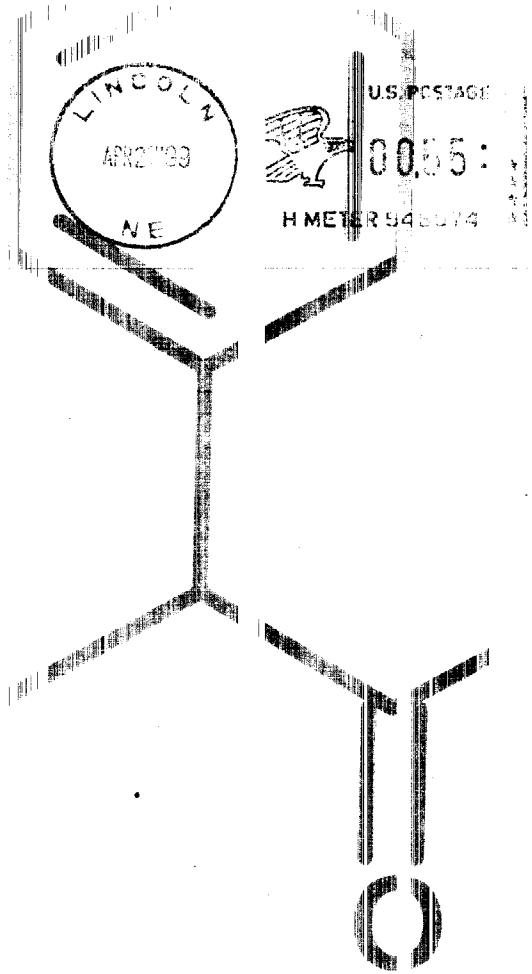

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